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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/707,117	WOLFF ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,7,11,12,16-20,24,25,28-31,34-36 and 39-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,11,12,16-20,24,25,28-31,34-36 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-28-05 has been entered.

Applicant's arguments filed 1-28-05 have been fully considered but they are not persuasive. Claims 4, 5, 8-10, 13-15, 21-23, 26, 27, 32, 33, 37 and 38 remain canceled. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 remain pending and under consideration. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicants' response should clearly distinguish the arguments to new matter, enablement and indefiniteness. For example, as written in the first paragraph under the heading "Rejection of the claims under 35 USC 112" on pg 5 of the response filed 1-28-05, all the new matter and indefiniteness rejections have been combined. The arguments for the indefiniteness rejection may refer to the new matter arguments, but the arguments cannot be combined. The arguments have also erroneously mentioned 112, second paragraph, under 112, first paragraph, rejections (see pg 6, first lines of

paragraphs 1 and 2; pg 7, last full paragraph). The arguments do not specifically address new matter rejection. Please begin each response with support for any amendments made to the claims followed by a heading for claim objections, new matter, enablement, indefiniteness, 102, 103 and double patenting. Each rejection every heading must be argued. Arguments may be repeated or may reference arguments in preceding paragraphs, but cannot be combined or absent.

Claim Objections

The previous objections have been withdrawn in view of the amendments to the claims.

The phrase "delivering" and "expressing the polynucleotide" in claim 1 should be clearly set forth as steps in the claim because they are written as active steps.

The preamble of claim 1 should parallel the body of the claim, i.e. the preamble should be directed toward a method of expressing a polynucleotide in a skeletal muscle cell in the limb of a mammal.

The phrase "and expressing the polynucleotide" in claim 39, lines 10-11, should be clearly set forth as a step in the claim because it is an active step in the method.

The preamble of claim 39 should parallel the body of the claim, i.e. the preamble should be directed toward a method of expressing a polynucleotide in a skeletal muscle cell in the limb of a mammal.

Claim Rejections - 35 USC ' 112

New Matter

1. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 as newly amended are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The term "non-invasive" in claims 1 and 39 remains new matter. No explicit support can be found. "Invasive" can be defined two different ways. 1) "denoting a procedure requiring insertion of an instrument or device into the body through the skin or a body orifice..." (see Stedman's Medical Dictionary definition attached) or 2) "to affect injuriously and progressively" (see Merriam-Webster Online Dictionary definition attached). The specification does not implicitly support applying pressure without inserting an instrument or device into the body through the skin. It is not readily apparent that the pressure applied in Example 1 was applied without "inserting an instrument into the body through the skin" because the cuff was applied while the inside of the leg was exposed; it is not readily apparent that the cuff was applied outside of the surgical area. The specification also describes using clamps (Example 8) which are inserted inside the leg but do not cause damage to the leg. Therefore, the specification

does not implicitly support applying pressure without insertion of an instrument or device into the body as encompassed by "non-invasive."

Applicants argue:

> "The action states 'The specification does not implicitly support applying pressure without inserting an instrument of device into the body through the skin.' The action further provides a definition of invasive obtained from Steadman's Medical Dictionary. This definition corresponds with the description provided by the Applicants' specification (page 5 lines 13-24). Applicants have not claimed a non-invasive injection device. Applicants further acknowledge that some of their examples include the much more invasive use of clamps applied directly to limb vessels. Comparing example 10 (starting on page 32) with example 8 (starting on page 31) demonstrates that using a cuff can substitute for invasively clamping individual vessels in occluding blood flow. The use of the non-invasive cuffs a significant improvement over using individual clamps because it makes the method much less invasive, faster and easier to perform, and provides improved occlusion of blood flow to and from the limb."

Applicants' arguments are not persuasive. The examiner provided two definitions of "invasive" with different scopes and concluded from the specification that applying "non-invasive" pressure as claimed was limited to a cuff as in Example 1. Applying a cuff as described in the specification has a much smaller scope than applying "non-invasive" pressure as claimed. Therefore, the broader scope of applying "non-invasive" pressure as claimed does not have support in the specification as originally filed.

The phrase "polynucleotide encoding a protein operably linked to a promoter in a solution" as newly amended in claim 1 is new matter. No support has been provided for the breadth of any "solution" and none can be found.

The phrase "polynucleotide encoding an expressible sequence operably linked to a promoter in a solution" as newly amended in claim 39 is new matter. No support has been provided for "expressible sequence" or the breadth of any "solution" and none can be found.

Enablement

The enablement regarding injecting the polynucleotide to the limb proximally to the applied pressure and obtaining delivery of the polynucleotide to the skeletal muscle cells of the limb distally to the applied pressure has been withdrawn in view of the amendments. Claim 1 as newly amended requires applying pressure to a limb so that blood flow is impeded, and injecting a polynucleotide into a blood vessel of the limb distal to the applied pressure, and delivered to the skeletal muscle cell in the limb distal to the applied pressure. Claim 39 as newly amended requires applying pressure to a limb so that blood flow is impeded, and inserting a polynucleotide into a blood vessel of the limb distal to the applied pressure and delivering the polynucleotide to the skeletal muscle cells of the limb distal to the applied pressure.

The rejection regarding why or when an immunosuppressive agent is administered has been withdrawn in view of applicants' arguments. Potter (Annals of New York Acad. Sci., June 1999, Vol. 875, pg 159-174) taught using

immunosuppressive agent to prevent antibodies against transgene products, a problem inherent to all gene therapy (see abstract).

In the office action of 8-14-04, it was determined that pg 9, lines 8-12, taught delivering gene products such as growth hormone, factor IX, etc. could be used to determine the amount of a secreted protein that a gene delivery procedure can produce and that "the reporter gene product can be assayed in a small amount of blood." Example 8, pg 31, teaches delivering plasmid encoding Factor IX to determine the amount of secreted protein in the sera and muscle. Therefore, the specification supports using marker genes or therapeutic genes for delivery to skeletal muscle cells as markers to determine the amount of protein expressed in skeletal muscle cells.

The rejection regarding the specification only teaching delivering DNA encoding a protein operably linked to a promoter has been withdrawn because the claims as newly amended require the polynucleotide encodes a protein operably linked to a promoter.

2. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a protein operably linked to a promoter and wherein said protein is expressed to detectable levels

in muscle cells of said limb, does not reasonably provide enablement for expressing a polynucleotide in skeletal muscle cells by injecting a viral vector into a blood vessel of a limb and applying a cuff proximal to the site of injecting. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claim 1 requires applying pressure to a limb so that blood flow is impeded, and injecting a polynucleotide into a blood vessel of the limb distal to the applied pressure, and delivered to the skeletal muscle cell in the limb distal to the applied pressure.

Claim 39 requires applying pressure to a limb so that blood flow is impeded, and inserting a polynucleotide into a blood vessel of the limb distal to the applied pressure and delivering the polynucleotide to the skeletal muscle cells of the limb distal to the applied pressure.

Claim 3 is dependent upon claim 1 and is directed toward applying non-invasive pressure to a limb, injecting a viral vector into a blood vessel of the limb distal to the applied pressure and obtaining expression in a skeletal muscle cell distal to the applied pressure. Claims 1 and 39 encompass using viral vectors.

In gene therapy, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art (Miller of record, 1995, FASEB J., Vol. 9, pages 190-199; Deonarain of record, 1998,

Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, 1st ¶; pg 65, 1st ¶, under Conclusion section; Verma of record, Sept. 1997, Nature, Vol. 389, pg 239-242; see entire article; pg 240, sentence bridging col. 2 and 3; Crystal of record, 1995, Science, Vol. 270, pg 404-410; pg 409).

Milas of record (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203) specifically taught applying a tourniquet to the leg of a rat passed under the inguinal ligament and injecting adenoviral particles to the femoral artery and vein distal to the applied pressure as claimed. Milas taught that applying pressure non-invasively and injecting an adenovirus distal to the applied pressure as encompassed by steps a and b of claims 1 and 39. Milas did not obtain protein expression in skeletal muscle cells distal to the applied pressure using an adenoviral vector. (pg 2198, Fig. 1A and B, see legend and tourniquet in Fig. 1A; pg 2201, col. 2, 1st full ¶).

While the tourniquet described in the instant application is not passed under the inguinal ligament as taught by Milas, Milas applied to tourniquet to the skin outside of the surgical area, thereby, applying pressure non-invasively as claimed. The method claimed is not limited to applying pressure non-invasively without applying pressure invasively, in the absence of a surgical procedure or without passing the applied pressure over a surgical area. Milas also used perfusion to allow some of the blood to flow out of the leg while the tourniquet blocked blood flow, which is different than the method described in the specification. However, the claims encompass blocking blood

flow using a tourniquet while allowing some blood to flow out of the limb using a perfusion pump as taught by Milas and are not limited to blocking blood flow in and out of the limb without allowing any blood to outflow from the limb. The method steps of Milas did not result in expression in skeletal muscles of the limb as claimed; therefore, the method steps claimed are not enabled for obtaining expression in skeletal muscle cells as broadly claimed. Applicants have not correlated the results of Milas with expected results when the perfusion pump is not used and the tourniquet is not passed under the inguinal ligament. The difference between passing the tourniquet under the inguinal ligament and not passing the tourniquet under the inguinal ligament would be insignificant to one of skill in the art. It is not readily apparent that injecting an adenovirus using the method in claim 1 (applying a cuff, injecting the vector 5 minutes later and removing the cuff two minutes later) would cause protein expression because Milas taught an adenovirus perfusing through the leg for 13 minutes did not cause expression (pg 2199, col. 1, 2nd full ¶, last sentence).

Ye of record (March 1, 2000, Human Gene Therapy, Vol. 11, pg 621-627) confirms that adenoviral vectors would not be expected to cause expression in skeletal muscle cells using the steps claimed. Ye taught administering adenoviral particles encoding LacZ to the portal vein/artery occluded with clamps did not result in expression in skeletal muscle.

Applicants again point to the declaration filed 5-9-03, which was found unpersuasive because the teachings in the declaration were not present in the specification and were essential to perform the method using adenovirus. Applicants argue the teachings in the declaration were present in the specification as originally filed. Applicants' arguments are not persuasive.

The combination of elements required to target the tissue of interest using adenovirus is essential to the claimed invention (based on Miller, Verma, Crystal, Deonarain, and Ye all of record). The specification suggests using papaverine (pg 5, lines 26-28; ¶ bridging pg 16-17) and "an enzyme [that] could digest the extracellular material" (¶ bridging pg 16-17). It is not readily apparent from the specification that applicants considered using both papaverine and collagenase as described in the declaration because the paragraph bridging pg 16-17 and pg 5, lines 26-28 only suggest using one compound that is papaverine or an enzyme and because Examples 1 and 8 only used papaverine.

Example 8 does not correlate to the results described in the declaration because example 8 required plasmid DNA and did not use collagenase while the declaration taught injecting $\underline{5x10^8}$ adenoviral particles/10 ml saline within 10 seconds after papaverine and collagenase. It is not readily apparent that merely replacing the plasmid in Example 8 with adenovirus would provide the results described in Example 8 in the absence of collagenase. The concentration of $5x10^8$ adenoviral particles/10 ml saline

described in the declaration is not taught anywhere in the specification and is not readily apparent from the teachings of the specification. Pg 17, line 9, to pg 18, line 6, only describe the injection volume (ml, ml/body weight, ml/liver weight or ml/limb muscle weight) and the speed at which a vector is injected. Pg 17, line 9, to pg 17, line 25, does not correlate to the results described in the declaration because they are limited to injection volumes for non-viral vectors. In conclusion, the specification does not reasonably lead one of skill to the specific combination of injecting $5x10^8$ adenoviral particles/10 ml saline within 10 seconds after papaverine and collagenase. Therefore, the specification does not teach the essential elements required to obtain the results described in the declaration.

In addition, the claims are not limited to delivering adenovirus, or to delivering adenovirus in combination with papaverine and collagenase before injection, or to injecting the adenovirus within 10 seconds. Therefore, the data in the declaration does not correlate to the claims because the data in the declaration only represents a small species within the genus claimed.

Applicants argue the use of agents to increase vascular permeability should not be limited to one agent. Therefore, applicants appear to conclude that the specification as originally filed disclosed using the combination of papaverine and an enzyme as described in the declaration. Applicants' argument is not persuasive because the specification does not suggest using more than one compound that increases vascular

permeability because the two compounds may have a synergistic effect that is essential to obtain the necessary vascular permeability and because it would not have been readily apparent to one of skill would that applicants considered using the specific combination of papaverine and an enzyme together.

Applicants argue the volumes disclosed in the specification for non-viral vectors are enabling for non-viral vectors. Applicants' argument is not persuasive. The specification does not correlate the viral and non-viral vectors or teach the volume to use when injecting viral vectors. It is not readily apparent that the volumes disclosed in the specification apply to both viral and non-viral vectors. Applicants argue the "explicit number of viral particles to inject will be dependent on the amount of tissue to which the vector is to be delivered and can be readily determined by those practicing the art without undo experimentation. One need simply do routine experimentation to optimize the number of viral particles to include in the injection solution." Applicants' argument is not persuasive. The specification is silent regarding the number of viral particles to inject in the claimed method. Therefore, applicants' assertion that routine experimentation was required to determine the number is unfounded. In view of the art at the time of filing, which taught the combination of elements required to express a protein in the desired tissue using gene therapy was unpredictable, one of skill would have known that injecting $5x10^8$ adenoviral particles in the volume described in the declaration was essential to the invention but was not part of the original disclosure.

Indefiniteness

The rejection of claim 1 regarding whether the claim is intended to encompass injecting the polynucleotide anywhere in the limb and obtaining delivery distal to the site of applying pressure or if the claim is limited to injecting the polynucleotide into a limb distal to the site of the same limb to which pressure is applied and obtaining delivery of the polynucleotide distal to the site of pressure has been withdrawn in view of the amendment.

3. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The phrase "to a skeletal muscle cell of a mammal" in the preamble in claim 1 is not commensurate in scope with the phrase "to the skeletal muscle cell in the limb distal to the applied pressure" in step c of claim 1. The phrase ""the skeletal muscle cell in the limb distal to the applied pressure" in step c of claim 1 lacks antecedent basis. It is unclear if the claim is intended to deliver the polynucleotide to any skeletal muscle cell of mammal as in the preamble or to a skeletal muscle cell of a limb distal to the site of applying pressure as in the body of the claim.

Claim 1, step b), as newly amended is indefinite because the phrase "inserting the polynucleotide encoding a protein operably linked to a promoter in a solution into a blood vessel" lacks antecedent basis. The phrase in the body of the claim is not readily apparent from the preamble of the claim, which merely refers to "delivering a polynucleotide to a skeletal muscle cell of a mammal in vivo."

The phrase "applying non-invasive external pressure" in claim 1 and "applying pressure non-invasively" in claim 39 remain indefinite for reasons of record. "Invasive" can be defined two different ways. 1) "denoting a procedure requiring insertion of an instrument or device into the body through the skin or a body orifice..." (see Stedman's Medical Dictionary definition attached) or 2) "to affect injuriously and progressively" (see Merriam-Webster Online Dictionary definition attached). The specification does not teach which scope to use. It is not readily apparent that the methods used by applicants do not require inserting an instrument into the body through the skin because the cuff described in Example 1 was applied during a surgical procedure. It is not readily apparent that the cuff was applied outside of the surgical area (only on skin) and not over the surgical area. Therefore, it cannot be determined whether pressure that does not cause injury to the leg is encompassed by the phrase.

Applicants argue the phrases are limited to a cuff as in Example 8. Applicants' argument is not persuasive because the cuff was used during a surgical procedure and may have been applied over the surgical area. Overall, one of skill would not have

known which scope of "invasive" to use to determine the metes and bounds of applying pressure "non-invasively" as claimed.

The phrase "wherein said applying, said inserting, said delivering and said expressing the polynucleotide do not diminish subsequent use of the limb by the mammal" as newly amended in claim 39 remains unclear. It is unclear if the phrase is limited to the function of the limb after the procedure or if the phrase encompasses the diminished frequency of use of the limb. Pg 3, lines 13-19, and pg 25, lines 17-25, do not clarify the issue. Pg 3 refers to maintaining the function of the limbs after delivery of polynucleotides and applying pressure. Pg 25, lines 17-25, also refers to maintaining the function of the limbs after delivery of polynucleotides and applying pressure. It is not readily apparent from the specification that pg 3 or pg 25 encompasses the frequency of use of the limb. Applicants argue the two parameters are not distinct. applicants cite various teaching in the specification where applicants contemplate preventing ischemic tissue damage; however, the claim is not limited to preventing ischemic tissue damage. Pg 22, lines 26-29, teach obtaining minimal intimal changes in the arteries were observed but does not discuss the effect of the surgery or gene expression on the function or frequency of use of the limb. Pg 25, lines 17-20 teaches monkeys had full function of the limbs but does not teach the monkeys used their limbs as frequently as before the surgery. Pg 25, lines 22-24, teaches the monkeys were not in any discomfort but does not teach the monkeys used their limbs as frequently after

surgery. In fact, contrary to the claim, the monkeys must have had diminished use of the limb right after surgery.

The phrase "the polynucleotide encoding an expressible sequence operably linked to a promoter in a solution" in claim 39, step b) lacks antecedent basis.

The phrase ""the skeletal muscle cell of the limb distal to the applied pressure" in step b) of claim 39.

Claim Rejections - 35 USC '102

4. Claim 39 remains rejected under 35 USC 102(e) as being anticipated by Draijer-van der Kaaden (US Patent 6,495,131). '131 has priority back to July 13, 1998.

Draijer-van der Kaaden taught administering adenovirus to the femoral vein using a tourniquet around the groin, and fixed to the inguinal ligament (detailed description, ¶ 25; col. 17, lines 1-55). The adenovirus was perfused through the leg using a pump. The tourniquet impeded blood flow into and out of the blood vessel as claimed because it was wrapped around the leg and blocked the blood vessels. The tourniquet was "non-invasive" as claimed because it did not injure the leg. The method of Draijer-van Kadden resulted in expression in skeletal muscle cells as claimed because the adenovirus was perfused for 5 to 30 minutes (col. 17, line 19) and expression was obtained in skeletal muscle (Table II, col. 18).

The tourniquet of Draijer-van der Kaaden impedes inflow and outflow of blood through the limb as claimed because it is around the leg and blocking blood vessels. The claim encompasses using a tourniquet in combination with the perfusion pump described by Draijer-van der Kaaden.

Applicants argue the reference does not teach impeding inflow and outflow of blood. Applicants' argument is not persuasive and was specifically addressed in the last office action (see paragraph above).

Applicants argue '131 taught "no high uptake of IG.Ad.MLP.Luc by the liver or skeletal muscle of the isolated limb after ILP or intra-tumor injection" Therefore, it appears that applicants conclude '131 did not teach expression in skeletal muscle. Applicants' argument is not persuasive. Table II clearly shows skeletal muscle tissue had greater luciferase expression than liver and that 30 minutes of perfusion of the adenovirus caused greater expression in the skeletal muscle than 5 minutes.

5. Claim 39 remains rejected under 35 U.S.C. 102(a) as being anticipated by Von der Leyen (9-20-99, Human Gene Therapy, Vol. 10, pg 2355-2364) for reasons of record.

Von der Leyen taught administering naked plasmid DNA into the carotid artery while applying a sphygmomanometer to the skin of the limb (pg 2356 col. 2, Transfection procedure; pg 2360, Fig. 2, see 300). The sphygmomanometer impedes inflow and outflow of blood to the limb. While Von der Leyen did not explicitly teach

obtaining delivery to skeletal muscle as claimed, Von der Leyen implicitly taught obtaining delivery to skeletal muscle. Von der Leyen obtained expression in the layers of the carotid artery; therefore, the method of Von der Leyen inherently results in delivery beyond the blood vessel wall and into skeletal muscle as claimed because the carotid artery is surrounded by skeletal muscle. Inherency is also relied upon because Von der Leyen forced the DNA through the blood vessel wall (pg 2362, col. 1, line 14).

Applicants argue a sphygmomanometer has an inflatable cuff and a pressure gauge; however, Von der Leyen only used the pressure gauge of the sphygmomanometer. Applicants argue the sphygmomanometer was not used to apply pressure to the skin as claimed because "a sphygmomanometer will not fit on a rabbit limb" and "a percutaneous translumenal coronary angioplasty manometer was substituted in the method for pressures higher than 300 mmHg). Applicants' arguments are not persuasive. Von der Leyen clearly states the sphygmomanometer was used to monitor the pressure ("a commercially available sphygmomanometer was used to monitor pressure." sentence bridging pg 2356-2357). Nowhere does Von der Leyen teach the sphygmomanometer was dismantled or that only the pressure gauge of the sphygmomanometer was used. Since applicants argue a sphygmomanometer is defined as an inflatable cuff and a pressure gauge, Von der Leyen must have used to cuff applied to the skin to monitor pressure. Applicants' comments regarding the angioplasty manometer are irrelevant.

Applicants argue Von der Leyen did not inherently obtain delivery to skeletal muscle because the artery was "isolated," surrounded by a water impermeable polyethylene sheath, clamped at the proximal end of the sheath and ligated at the distal end of the sheath. Applicants' arguments are not persuasive. The artery may have been "isolated" during balloon angioplasty (last full ¶ on pg 2356), but Von der Leyen did not teach the artery being transfected was isolated (¶ bridging pg 2356-2357). Applicants' argument that the sheath, clamp and ligature would prevent leakage of the adenoviral vector to surrounding skeletal muscle is unfounded. The space between the clamp and the sheath or the ligature and the sheath would allow delivery of the adenovirus to the skeletal tissue surrounding the artery. The adenovirus that makes it through the arterial wall may also leak out from the sheath into the surrounding skeletal muscle tissue.

Applicants argue Von der Leyen is limited to obtaining delivery and expression to the tissues of the vessel wall itself. Applicants argument is not persuasive because the results show that pressure applied to the artery drove the DNA through every layer. The blood vessels were damaged by angioplasty and inherently had leakage into the surrounding skeletal muscle under high pressure delivery. Thus, Von der Leyen inherently delivered the DNA to skeletal muscle and obtained detectable levels of expression.

Claim Rejections - 35 USC ' 103

6. Claims 1-3, 6, 11, 12, 16, 17, 28, 30, 31, 34, 35, 36 and 39-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Budker (1998, Gene Therapy, Vol. 5, pg 272-276) in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) for reasons of record.

Budker taught administering naked plasmid DNA encoding marker protein into the external iliac artery of a rat, wherein all inflow and outflow of blood was blocked using microvessel clips applied to the external iliac, caudal epigastric, internal iliac and deferent duct arteries and veins (pg 273, Fig. 1). Administration resulted in marker protein expression in skeletal muscle cells of the leg (pg 274, col. 2, 1st full ¶). Budker also taught injecting collagenase, which is equivalent to applying immunosuppressive drugs because collagenase degrades the capillary membranes thereby decreasing the flow of blood through the immune system (i.e. immunosuppression). Budker did not teach applying pressure to the skin of the limb as claimed.

However, Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the epidermis of the leg (pg 2198, Fig. 1A, see tourniquet on rat). The tourniquet of Milas was used to completely block blood flow to and from the leg while a perfusion devise was used to deliver DNA to the leg.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into an

artery of a leg, in which blood flow to the leg had been completely occluded as taught by Budker wherein the blood flow to the leg was completely occluded using a tourniquet as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the microvessel clips with the tourniquet of Milas to reduce damage to the blood vessels, to eliminate surgical procedures and to save time.

Applicants argue "Milas does not result in delivery of nucleic acid to skeletal muscle as explicitly taught by Milas (page 2201, Col. 2)." Milas, pg 2201, col. 2, 1st full paragraph, taught no beta-gal staining was apparent in the muscular tissue of the perfused limb. However, Budker taught marker protein was expressed in skeletal muscle cells of the leg. Thus, Budker provides one of ordinary skill in the art at the time the invention was made with the means to express the protein in the skeletal muscle. Milas also allowed outflow of blood to the leg using the perfusion devise, while Budker did not. Thus, it would have been readily apparent that completely blocking blood flow from the leg as taught by Budker would provide expression in the skeletal muscle of the leg while allowing some outflow as taught by Milas would not. While Milas taught that the combination of a tourniquet that completely blocks blood flow to and from the leg and a perfusion devise that allows some outflow of blood from the leg failed to cause marker protein expression in skeletal muscle, one of ordinary skill in the art would have recognized that the tourniquet of Milas completely blocked blood flow to and from the

leg and could be used in other DNA delivery methods that require completely blocking blood flow to and from the leg.

Applicants' statement regarding impeding blood flow into and out of the limb is noted on pg 10. While Milas allows blood flow out of the leg using the perfusion devise, the tourniquet described by Milas impedes blood flow in to and out of the leg as claimed. Claim 39 encompasses impeding blood flow to and from the limb and allowing some blood flow out of the limb using a perfusion devise. Claim 39 is not limited to impeding all blood flow in to and out of the leg.

7. Claims 1-3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 39-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (US Patent 6,265,387, July 24, 2001) in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203).

Wolff taught delivering naked plasmid DNA to a clamped femoral artery and obtaining expression in the quadriceps (col. 17, Example 8). Some of the animals received subcutaneous administration of dexamethasone the day before surgery (col. 18, line 45), which is an immunosuppressive drug as, claimed. Wolff did not teach using a tourniquet.

However, Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the skin of the leg passed under the inguinal ligament (pg 2198, Fig. 1A, see tourniquet on rat and description in legend of Fig. 1B).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into an femoral artery of a rat using pressure to obtain expression in the quadriceps as taught by Wolff using a tourniquet applied to the skin of the leg as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using clamps of Wolff with using the tourniquet of Milas to reduce damage to the blood vessel and to eliminate time in surgery spent applying the clamps. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the adenoviral vector of Milas with the plasmid DNA of Wolff to prevent viral infection.

Applicants have not addressed this rejection.

Double Patenting

8. Claims 1-3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 39-42 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,265,387 in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) for reasons of record.

Wolff claimed delivering naked plasmid DNA to a bile duct, increasing the permeability of the bile duct and obtaining delivery and expression in the liver. Wolff did not claim delivering DNA to skeletal muscle as claimed.

However, Wolff taught clamps applied to the femoral artery increased permeability of the artery and taught delivering naked plasmid DNA to a clamped femoral artery and obtaining expression in the quadriceps (col. 17, Example 8). Some of the animals received subcutaneous administration of dexamethasone the day before surgery (col. 18, line 45), which is an immunosuppressive drug as claimed.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into a vessel, increasing permeability and obtaining expression as claimed by Wolff wherein the vessel was a femoral artery, the permeability was increased using clamps and the DNA was delivered to skeletal muscle as taught in the specification of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated to inject the femoral artery instead of the bile duct as suggested in the specification of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated to use clamps to increase permeability in light of the disclosure of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated to deliver DNA to skeletal muscle instead of the liver as in claim 1 of Wolff because Wolff suggested delivering DNA to skeletal muscle cells. The combined teachings of the claim and disclosure of Wolff did not teach using a tourniquet.

Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the skin of the leg and passed under the inguinal ligament (pg 2198, Fig. 1A, see tourniquet on rat and legend of Fig. 1B).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into the femoral artery of a rat using pressure to deliver the DNA to the quadriceps as taught by the combined teachings of the claim and disclosure of Wolff using a tourniquet as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using clamps with using the tourniquet of Milas to reduce damage to the blood vessel and to eliminate time in surgery spent applying clamps. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the adenoviral vector of Milas with naked plasmid DNA to prevent viral infection.

Applicants argue Milas did not impede blood flow into and out of the limb as claimed. applicants' argument is not persuasive. While Milas allows blood flow out of the leg using the perfusion devise, the tourniquet described by Milas impedes blood flow in to and out of the leg as claimed. The claims encompass impeding blood flow to and from the limb and allowing some blood flow out of the limb using a perfusion devise. The claims are not limited to impeding all blood flow in to and out of the leg.

9. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 as newly amended are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,627,616 in view of the disclosure of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) for reasons of record.

Claim 2 of '616 requires injecting naked DNA into a blood vessel and increasing the permeability of the blood vessel by increasing the pressure inside the vessel and obtaining delivery to cells outside of the blood vessel. Claim 3 requires inserting papaverine into the blood vessel. '616 did not claim delivering DNA to skeletal muscle as claimed.

However, '616 taught injecting plasmid DNA into the iliac artery using clamps "to block both the outflow and inflow of the blood to the leg" and L-NMMA and obtaining expression in the quadriceps (col. 9, lines 23-44).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into a blood vessel, increasing permeability and obtaining delivering the DNA to a cell outside of the blood vessel as claimed in '616 wherein the vessel was the iliac artery, the permeability was increased using clamps and L-NMMA the DNA was delivered and expressed in the quadriceps as taught in the specification of '616. One of ordinary skill in the art at the time the invention was made would have been motivated to inject the

iliac artery because the specification of '616 expressly taught injecting the iliac artery was part of the invention. One of ordinary skill in the art at the time the invention was made would have been motivated to "block both the outflow and inflow of the blood to the leg" because the specification of '616 expressly taught blocking both the outflow and inflow of the blood to the leg was part of the invention. The combined teachings of the claim and disclosure of Wolff did not teach using a tourniquet.

Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the skin of the leg and passed under the inguinal ligament (pg 2198, Fig. 1A, see tourniquet on rat and legend of Fig. 1B).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into the iliac artery of a rat using pressure and L-NMMA to deliver the DNA to the quadriceps as taught by the combined teachings of the claim and disclosure of '616 using a tourniquet as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using clamps of '616 with using the tourniquet of Milas to reduce damage to the blood vessel and to eliminate time in surgery spent applying clamps. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the adenoviral vector of Milas with naked plasmid DNA to prevent viral infection.

Applicants argue Milas did not impede blood flow into and out of the limb as claimed. Applicants argue Milas did not deliver DNA to the skeletal muscle. Therefore, applicants conclude there "can not a been [sic] a reasonable expectation of success" (pg 11, line 5 of response). Applicants' arguments are not persuasive. While Milas allows blood flow out of the leg using the perfusion devise, the tourniquet described by Milas impedes blood flow in to and out of the leg as claimed. The claims encompass impeding blood flow to and from the limb and allowing some blood flow out of the limb using a perfusion devise. The claims are not limited to impeding all blood flow in to and out of the leg.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER